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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/602,812	06/23/2000	Mark Sliwkowski	P1467R2	9612

7590 01/02/2004

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	24

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/602,812	SLIWKOWSKI, Mark	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-9,12,13,16-22,24-29,34 and 60-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9,12,13,16-22,24-29,34 and 60-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The amendments filed May 6, 2003 and March 24, 2003 are acknowledged.

Claims 27, 34, 60 and 61 were amended. Claim 63 was added.

Claims 1, 2, 4-9, 12, 13, 16-22, 24-29, 34 and 60-63 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The allowance of claim 62 is withdrawn in view of new grounds of rejection.

Information Disclosure Statement

4. Copies of signed Information Disclosure Statements (PTO-1449) filed Aug. 29, 2000, Jan. 24, 2001, Oct. 30, 2001, July 17, 2002, Feb. 27, 2003, and April 28, 2003 are included with this Office action.

Rejections Withdrawn:

5. The rejection of claims 1-2, 4-6, and 20 under 35 U.S.C. 102(e) as being anticipated by Hudziak or Arakawa et al., as evidenced by Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, or Earp et al., Breast Cancer Research and Treatment, Vol. 35, pages 115-132, 1995 (IDS #38) is withdrawn upon further consideration.

6. The rejection of claims 7 and 60 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn upon further consideration and in favor of new grounds of rejection.

New Grounds of Rejection:

7. Claims 27-29, 34 and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the amendment to claims 27, 34 and 60 introduces new matter into the specification.

The amendment introduces new matter into the specification, because the specification only provides support for contemplation of methods where the antibody to be used in the claimed methods blocks ligand activation of an ErbB receptor *substantially* more effectively than monoclonal antibody 4D5. Thus, the specification describes methods where there is substantial difference between the activity of the antibody to be used in the claimed methods compared to the activity of monoclonal activity 4D5, whereas the claimed methods are drawn to methods where the antibody to be used in the claimed methods may exhibit even a very slight difference in activity when compared to monoclonal antibody 4D5.

Secondly, the claimed inventions lack written description because the specification describes the term "monoclonal antibody 4D5" as an antibody that has antigen binding residues of, or derived from, the murine 4D5 antibody (ATCC CRL 10463). Therefore, the monoclonal antibody 4D5, as currently recited in the claims, may be one that has very little in common structurally with the murine antibody 4D5 (ATCC CRL 10463), and may have very low binding affinity for Her-2 and may not have any effect on cell proliferation. For example, the specification also cites U.S. Patent 5,821,337, which describes humanized versions of the murine antibody 4D5 (ATCC CRL 10463), where some of the humanized versions do not have any effect or very little effect on cell proliferation. In view of the definition of the 4D5 antibody, it appears that the claimed methods comprise the use of an antibody that may be functionally compared to an antibody that has very little in common with the one antibody that was used in working examples (trastuzumab, huMab 4D5-8). Therefore, the examples in the specification are not representative of the full scope of the claims.

Therefore, the claims are not supported by the specification as originally filed because the amendment introduces new matter, and because the full scope of the claimed methods, comprising the administration of inadequately described antibodies, is not represented by the one species of monoclonal antibody 4D5 having ATCC number CRL 10463. Therefore, it does not appear that applicant was in possession of the invention as claimed at the time the application was filed.

8. Claims 1, 2, 4-9, 12, 13, 16-22, 24-26, 61, 62 and 63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s)

contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the specification lacks written description of "monoclonal antibody 2C4".

Furthermore, the specification fails to provide written description of antibodies which block ligand activation of an ErbB receptor more effectively than monoclonal antibody 4D5, in view of the specification's definition of "monoclonal antibody 4D5".

Claims that recite monoclonal antibody 2C4 are also not described because the definition of this antibody is very broad and includes variants of monoclonal antibody 2C4 (ATCC HB12697), such as antibodies that have antigen binding residues of, or derived from the murine monoclonal antibody 2C4 (ATCC HB12697). In view of the broad definition, which includes antibodies with antigen binding residues that are "derived from" murine monoclonal antibody 2C4 (ATCC HB12697) without saying how many, or which, or in which arrangement, these residues are "derived from" murine monoclonal antibody 2C4 (ATCC HB12697), the term monoclonal antibody 2C4 without the reference ATCC number appears to refer to almost any antibody that might bind to Her-2.

Therefore, the claims are not supported by the specification as originally filed because the full scope of the claimed methods, comprising the administration of inadequately described antibodies, is not represented by the one species of monoclonal 2C4 antibody having ATCC number HB12697. Therefore, it does not appear that applicant was in possession of the invention as claimed at the time the application was filed.

9. Claims 1, 2, 7, 12, 13, 16, 17 and 20 rejected under 35 U.S.C. 102(e) as being anticipated by Greene et al., US Patent 5,824,311, published October 20, 1998 (IDS # 8), as evidenced by Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993.

The claimed inventions are drawn to methods of treating cancer in a human, wherein the cancer expresses epidermal growth factor receptor (EGFR) and ErbB2 comprising administering an antibody that binds ErbB2 and blocks binding of monoclonal antibody 2Cr o ErbB2.

Greene teaches a method of treating a patient, which includes humans, by administering a therapeutically effective amount of an antibody that binds ErbB2 and blocks ligand activation of an ErbB receptor. Specifically, Greene teaches that the p185 oncogene (which is the same as ErbB2) has been found active in lung adenocarcinoma, (an example of a tumor that expresses both erbB2 and EGFR) and further provides a method of using monoclonal antibodies which bind to ErbB2 to treat mammalian cancer tumors which express a translation of the neu oncogene on their surfaces (see column 3, line 50-column 5). The antibody of Greene et al. is not conjugated to a cytotoxic compound.

While Greene et al. does not explicitly recite that the cancer that is treated expresses or overexpresses EGFR, or overexpresses an ErbB ligand, including TGF-alpha, numerous cancers which express ErbB2 inherently co-express, or concurrently overexpress EGFR, and/or the ErbB ligand TGF-alpha. See Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, page 278, column 2, which determines that many ErbB2 positive patients also overexpress EGFR and that the ErbB ligand TGF-alpha is expressed at higher levels in malignancies.

This rejection is maintained and applied newly to claims 16 and 17, because antibodies may block binding of monoclonal antibody 2C4 by binding to the epitope that 2C4 binds to or by

acting on the antigen to make the epitope disappear. In the case of Greene, the preferred antibody is monoclonal antibody 7.16.4, which is an antibody that binds to a similar epitope on Her-2 that monoclonal antibody 4D5 binds to. The monoclonal antibody 4D5 causes internalization of erbB2. Therefore, absent evidence to the contrary the Greene antibody is one which would block binding of monoclonal antibody 2C4.

Alternatively, because the phrase monoclonal antibody 2C4 is so broad as to encompass any antibody that may happen to contain a residue in common with residues derived from the murine monoclonal antibody (ATCC HB12697), the phrase blocking binding of monoclonal antibody 2C4 may refer to the blocking of almost any antibody.

10. Claims 1, 2, 4, 7, 16, 17, 20, 24-26, 28, 29, 34, and 60-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak (U.S. Patent 5,725,856; issued 03/1998; effective filing date 01/1988) and Jardines (supra); in view of Sliwkowsky (Sliwkowsky, M.X. et al, J. Biol. Chem. 269: 14661-14665, 1994; IDS) or Klapper (Klapper, L.N. et al. Oncogene, 14: 2099-2109, 1997; IDS); and further in view of Plowman (U.S. Patent 5,804,396; issued 09/1998; effective filing 10/1994; IDS) or Greene (U.S. Patent 6,417,168; issued 07/2002; effective filing 03/1998; IDS).

The claimed inventions are drawn to methods for the treatment of cancers that express both EGFR and ErbB2, comprising the administration of antibodies that inhibit bind ErbB2 and block ligand activation of an ErbB receptor. Hudziak teaches methods of inhibiting the growth of tumor cells, by administering to a patient antibodies capable of inhibiting Her2 (ErbB2) function, and teaches methods of inhibiting the growth of tumor cells that overexpress a growth

factor receptor (see col. 4, lines 3-31). Hudziak is silent on the question of treating a subgroup of patients that express both EGFR and ErbB2. Jardines, however, teaches that patients with breast cancer who coexpress EGFR and ErbB2 had the shortest survival time of all the different subgroups of patients. Therefore, Jardines teaches that such a subgroup of patients is known to exist and, because of their shorter survival time, teaches a motivation to treat such patients (see page 278, col. 2). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used anti ErbB2 antibodies that inhibited the function of ErbB2 for the treatment of cancers that express both EGFR and ErbB2.

While the combination of Huziak and Jardines teaches generally methods for the treatment of cancers expressing both EGFR and ErbB2, comprising the use of antibodies that bind to ErbB2, and Hudziak contemplates antibodies that bind to ErbB2 and inhibit ligand binding to an ErbB growth factor receptor, or the down regulation of the growth factor (see col.5, lines 38-64), the combination of Hudziak and Jardines fail to specifically teach methods comprising the use of antibodies that inhibit the formation of an ErbB hetero-oligomer. However, such antibodies are known in the art, as evidenced by the teachings of Sliwkowsky that monoclonal antibody 2C4 inhibits the activation of ErbB2 by heregulin (see page 14663, 1st col.). Also, Klapper teaches antibodies that bind to ErbB2 and inhibit interaction of ErbB2 with other ErbB receptors (see pages 2102 –2105). Additionally, the prior art, as evidenced by Plowman, Akita and Greene, recognizes that the inhibition of ErbB2 oligomerization with other ErbB receptors is a therapeutic target for the treatment of cancer. Plowman teaches thereapeutic agents that inhibit signal transduction by Her-2 heterodimers (see abstract and col. 4, lines 31-49). Greene teaches methods for treatment of cancer comprising administering a peptide that

inhibits the formation of ErbB protein dimers, where the dimers may be heterodimers (see claims 1 and 14; and col. 9, lines 15-21).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the antibodies of either Sliwkowsky or Klapper in the method of Hudziak for the treatment of cancers that express both EGFR and ErbB2. One would have been motivated to use antibodies that inhibited ligand activation of an ErbB receptor in view of the fact that the art recognized that ErbB2 was activated by the formation of heterodimers and that ErbB2 activation plays a role in the growth of cancer cells.

Claims 24 -26 are drawn to methods reciting dosages and dosage schedules. However, the ability to establish treatment regimens is well known to those of ordinary skill in the art. Thus, it would have been prima facie obvious to one of ordinary skill in the art to have modified the methods of either Hudziak to include treatment regimens.

11. Claims 1, 18 19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak et al., US Patent 5,725,856, published March 10, 1998, and Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, in view of Sliwkowsky (Sliwkowsky, M.X. et al, J. Biol. Chem. 269: 14661-14665, 1994) or Klapper (Klapper, L.N. et al. Oncogene, 14: 2099-2109, 1997); and further in view of Plowman (U.S. Patent 5,804,396; issued 09/1998; effective filing 10/1994) or Greene (U.S. Patent 6,417,168; issued 07/2002; effective filing 03/1998), as applied to claim 1 above; and further in view of Grim et al., Am. J. Respir. Cell Mol. Biol., Vol. 15, pages 348-354, September 1996).

The claimed methods are interpreted to be drawn to methods using antibody fragments.

The combination of Hudziak and Jardines is silent on methods of using antibody fragments in methods of treatment. However, Grim et al. teaches a method of treating lung cancer by administering an antibody fragment which binds to ErbB2 (see abstract, and especially pages 350 and 353), thus teaching that the ErbB2 receptor is a therapeutic target in lung cancer and that antibody fragments may be used for treatment purposes. Therefore it would be *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to treat human lung cancer patients with an ErbB2 antibody, and it would have been prima facie obvious to one of ordinary skill in the art to use fragments of the antibodies of Hudziak in methods of treatment.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1, 2, 4-9, 16-22, 24-27, and 60-63 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 and 22-31 of copending Application No. 09/602,800. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of Application No.

09/602,800 are drawn to methods for treating cancer with an antibody that inhibits ligand activation of an ErbB receptor, and uses the monoclonal antibody 2C4.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
December 29, 2003

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